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Poly(L-lysine) has different membrane transport and drug-carrier properties when complexed with heparin.

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Methotrexate (MTX) conjugated to a Mr 3000 poly(L-Lys) markedly inhibits the growth of Pro-3 MtxRII5-3 Chinese hamster ovarian cells, a mutant line known to be drug resistant because of defective MTX transport. In these cells, membrane transport of [3H]MTX-poly(Lys) is sharply decreased by addition of 0.5- to 2.5-fold heparin but remains at 15-20% of control in 2.5- to 50-fold heparin excess. Heparin addition at first markedly inhibits but, at high concentration, restores the growth inhibitory effect of MTX-poly(Lys). In excess heparin, MTX-poly(Lys) is transported as a heparin complex. Because reduced transport (15-20%) is sufficient to cause a 90% inhibition of cell growth, MTX-poly(Lys) apparently gains pharmacologic potency when compared to heparin. This gain can be related to a greater inhibitory effect on dihydrofolate reductase and to a different mode of transport. The inhibitory effect of MTX-poly(Lys) on dihydrofolate reductase in vitro is increased nearly 100-fold in the presence of excess heparin but remains less than that of free MTX. Unlike that of MTX-poly (Lys), the transport of MTX-poly(Lys)-heparin has the characteristics and efficiency of a receptor-mediated process. It proceeds by endocytosis but is not, as in the case of uncomplexed conjugate, followed by the intracellular generation of pharmacologically active breakdown products that would account for cytotoxicity. These observations raise the possibility that at least part of the MTX-poly(Lys)-heparin reaches cellular dihydrofolate reductase in the form of macromolecular complexes that escape from entrapment in endocytotic structures. Our data illustrate a way to overcome drug resistance by taking advantage of the specific uptake of a macromolecular drug carrier. They offer a method of drug delivery in which heparin improves selectivity and decreases the unwanted toxicity inherent to polycationic carriers.

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